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Signed Andrew Gerry

Dated 15 October 1999

Patents Form 1/77

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1/77

04NOV98 E402111-1 001030
P01/7700 0.00 - 9824062.5

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The Patent Office

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1. You — GL/PG3602

2. Pat 9824062.5
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-3 NOV 1998

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

GLAXO GROUP LIMITED
GLAXO WELLCOME HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX
UB6 ONN
GB

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its corporation

GB 07358 7003

4 Title of the invention

CHEMICAL COMPOUNDS

5 Name of your agent *(if you know one)*

GRAHAM LANE (SEE CONTINUATION SHEET)

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GLAXO WELLCOME PLC
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UB6 ONN, GB

Patents ADP number *(if you know it)*

7164510001

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

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YES

See note (d))

Patents Form 1/77

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Continuation sheets of this form	1
Description	20
Claim(s)	4
Abstract	-
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10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**

Signature **MICHAEL J STOTT** **03 November 1998**

AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

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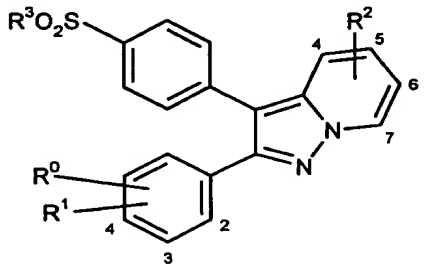
CHEMICAL COMPOUNDS

This invention relates to pyrazolo[1,5-a]pyridine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

The enzyme cyclooxygenase (COX) has recently been discovered to exist in two isoforms, COX-1 and COX-2. COX-1 corresponds to the originally identified constitutive enzyme while COX-2 is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. Prostaglandins generated by the action of COX have both physiological and pathological roles. It is generally believed that COX-1 is responsible for the important physiological functions such as maintenance of gastrointestinal integrity and renal blood flow. In contrast the inducible form, COX-2, is believed to be responsible for the pathological effects of prostaglandins where rapid induction of the enzyme occurs in response to such agents as inflammatory agents, hormones, growth factors and cytokines. A selective inhibitor of COX-2 would therefore have anti-inflammatory, anti-pyretic and analgesic properties, without the potential side effects associated with inhibition of COX-1. We have now found a novel group of compounds which are both potent and selective inhibitors of COX-2.

The invention thus provides the compounds of formula (I)



(I)

and pharmaceutically acceptable derivatives thereof in which:

R^0 and R^1 are independently selected from H, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{1-6}alkoxy substituted by one or more fluorine atoms;

R^2 is H, C_{1-6}alkyl, C_{1-6}alkyl substituted by one or more fluorine atoms, C_{1-6}alkoxy, C_{1-6}hydroxyalkyl, SC_{1-6}alkyl, C(O)H, $C(O)C_{1-6}$alkyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxy substituted by one or more fluorine atoms; and
R^3 is C_{1-6}alkyl or NH_2.

By pharmaceutically acceptable derivative is meant any pharmaceutically acceptable salt, solvate or ester, or salt or solvate of such ester, of the compounds of formula (I), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be the physiologically acceptable salts, but other salts may find use, for example in the preparation of compounds of formula (I) and the physiologically acceptable salts thereof.

Suitable pharmaceutically acceptable salts of the compounds of formula (I) include acid addition salts formed with inorganic or organic acids, preferably inorganic acids, e.g. hydrochlorides, hydrobromides and sulphates.

The term halogen is used to represent fluorine, chlorine, bromine or iodine.

The term 'alkyl' as a group or part of a group means a straight or branched chain alkyl group, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group.

In one aspect of the invention R^0 is at the 3- or 4- position of the phenyl ring, as defined in formula (I).

In another aspect of the invention R^2 is at the 6- position of the pyridine ring, as defined in formula (I).

In another aspect of the invention R^0 and R^1 are independently H, halogen, C_{1-6}alkyl, or C_{1-6}alkoxy.

In another aspect of the invention R^2 is C_{1-6}alkyl substituted by one or more fluorine atoms.

In another aspect of the invention R^3 is C_{1-3}alkyl or NH_2.

Within the invention there is provided one group of compounds of formula (I) (group A) wherein: R^0 and R^1 are independently H, halogen, C_{1-6}alkyl, or C_{1-6}alkoxy; R^2 is C_{1-3}alkyl substituted by one or more fluorine atoms; and R^3 is C_{1-3}alkyl or NH_2.

Within group A, there is provided a further group of compounds (group A1) wherein: R^0 and R^1 are independently H, F, Cl, C_{1-3}alkyl (e.g. methyl), or C_{1-3}alkoxy (e.g. ethoxy); R^2 is C_{1-3}alkyl substituted by one or more fluorine atoms (e.g. trifluoromethyl); and R^3 is methyl or NH_2.

Within group A1, there is provided a further group of compounds (group A2) wherein: R^0 is F, Cl, or C_{1-3}alkyl (e.g. methyl) or C_{1-3}alkoxy (e.g. ethoxy); R^1 is H; R^2 is C_{1-3}alkyl substituted by one or more fluorine atoms (e.g. trifluoromethyl); and R^3 is methyl or NH_2.

Within groups A, A1 and A2 there are provided further groups of compounds wherein R^0 is at the 3- or 4- position of the phenyl ring, and R^2 is at the 6- position of the pyridine ring, as defined in formula (I).

It is to be understood that the present invention encompasses all isomers of the compounds of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures).

Preferred compounds of the invention are:
4-[2-(3-fluoro-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl]-benzenesulfonamide;
2-(3-fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridine;
4-[2-(4-ethoxy-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl]-benzenesulfonamide;
4-[2-(4-fluoro-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl]-benzenesulfonamide;
2-(4-fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridine;
4-(2-phenyl-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl)-benzenesulfonamide;
3-(4-methanesulfonyl-phenyl)-2-phenyl-6-trifluoromethyl-pyrazolo[1,5-a]pyridine;

4-[2-(4-methyl-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl]-benzenesulfonamide;
and pharmaceutically acceptable derivatives thereof.

Compounds of the invention are potent and selective inhibitors of COX-2. This activity is illustrated by their ability to selectively inhibit COX-2 over COX-1.

In view of their selective COX-2 inhibitory activity, the compounds of the present invention are of interest for use in human and veterinary medicine, particularly in the treatment of the pain (both chronic and acute), fever and inflammation of a variety of conditions and diseases. Such conditions and diseases are well known in the art and include rheumatic fever; symptoms associated with influenza or other viral infections, such as the common cold; lower back and neck pain; headache; toothache; sprains and strains; myositis; neuralgia; synovitis; arthritis, including rheumatoid arthritis; degenerative joint diseases, including osteoarthritis; gout and ankylosing spondylitis; tendinitis; bursitis; skin related conditions, such as psoriasis, eczema, burns and dermatitis; injuries, such as sports injuries and those arising from surgical and dental procedures.

The compounds of the invention may also be useful for the treatment of other conditions mediated by selective inhibition of COX-2.

For example, the compounds of the invention may inhibit cellular and neoplastic transformation and metastatic tumour growth and hence be useful in the treatment of certain cancerous diseases, such as colonic cancer.

Compounds of the invention may also prevent neuronal injury by inhibiting the generation of neuronal free radicals (and hence oxidative stress) and therefore may be of use in the treatment of stroke; epilepsy; and epileptic seizures (including grand mal, petit mal, myoclonic epilepsy and partial seizures).

Compounds of the invention also inhibit prostanoid-induced smooth muscle contraction and hence may be of use in the treatment of dysmenorrhoea and premature labour.

Compounds of the invention inhibit inflammatory processes and therefore may be of use in the treatment of asthma, allergic rhinitis and respiratory distress syndrome; gastrointestinal conditions such as inflammatory bowel disease, Chron's disease, gastritis, irritable bowel syndrome and ulcerative colitis; and

the inflammation in such diseases as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, type I diabetes, myasthenia gravis, multiple sclerosis, sorcoidosis, nephrotic syndrome, Bechet's syndrome, polymyositis, gingivitis, conjunctivitis and myocardial ischemia.

Compounds of the invention may also be useful in the treatment of ophthalmic diseases such as retinitis, retinopathies, uveitis and of acute injury to the eye tissue.

Compounds of the invention may also be useful for the treatment of cognitive disorders such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease and Creutzfeldt-Jakob disease), and vascular dementia (including multi-infarct dementia), as well as dementia associated with intracranial space occupying lesions, trauma, infections and related conditions (including HIV infection), metabolism, toxins, anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.

According to a further aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by selective inhibition of COX-2.

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by selective inhibition of COX-2 which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative.

According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment of a condition which is mediated by selective inhibition of COX-2, such as an inflammatory disorder.

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from an inflammatory disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

It will be appreciated that the compounds of the invention may advantageously be used in conjunction with one or more other therapeutic agents. Examples of suitable agents for adjunctive therapy include pain relievers such as a glycine antagonist, a sodium channel inhibitor (e.g. lamotrigine), a substance P antagonist (e.g. an NK_1 antagonist), acetaminophen or phenacetin; a matrix metalloproteinase inhibitor; a nitric oxide synthase (NOS) inhibitor (e.g. an iNOS or an nNOS inhibitor); an inhibitor of the release, or action, of tumour necrosis factor α; an antibody therapy (e.g. a monoclonal antibody therapy); a stimulant, including caffeine; an H_2-antagonist, such as ranitidine; a proton pump inhibitor, such as omeprazole; an antacid, such as aluminium or magnesium hydroxide; an antiflatulent, such as simethicone; a decongestant, such as phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, epinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antitussive, such as codeine, hydrocodone, carmiphen, carbetapentane, or dextramethorphan; a diuretic; or a sedating or non-sedating antihistamine. It is to be understood that the present invention covers the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof in combination with one or more other therapeutic agents.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I) and their pharmaceutically acceptable derivatives.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets (including sub-lingual tablets), capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative.

Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

As stated above, the compounds of the invention may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a

pharmaceutically acceptable derivative thereof together with a further therapeutic agent.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

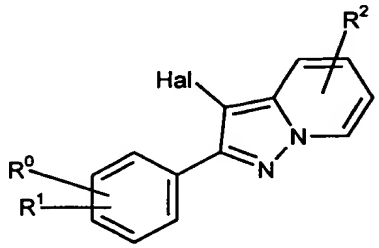
When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A proposed daily dosage of a compound of formula (I) for the treatment of man is 0.01mg/kg to 500mg/kg, such as 0.05mg/kg to 100mg/kg, e.g. 0.1mg/kg to 50mg/kg, which may be conveniently administered in 1 to 4 doses. The precise dose employed will depend on the age and condition of the patient and on the route of administration. Thus, for example, a daily dose of 0.25mg/kg to 10mg/kg may be suitable for systemic administration.

Compounds of formula (I) and pharmaceutically acceptable derivatives thereof may be prepared by any method known in the art for the preparation of compounds of analogous structure.

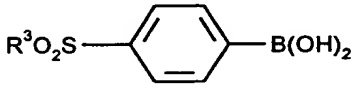
Suitable methods for the preparation of compounds of formula (I) and pharmaceutically acceptable derivatives thereof are described below. In the formulae that follow R^0 to R^3 are as defined in formula (I) above unless otherwise stated; Hal is a halogen, such as Br or I; X^- is a counterion, such as I^-; and alkyl is as previously defined.

Thus according to a first process (A), compounds of formula (I) may be prepared by reacting a compound of formula (II)



(II)

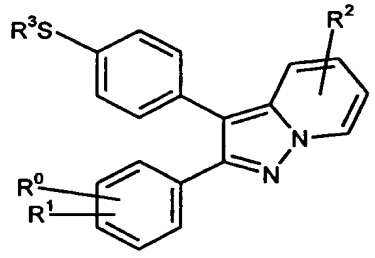
or a protected derivative thereof with a boronic acid of formula (III)



(III)

or a suitable derivative thereof in the presence of a suitable transition metal catalyst. Suitable derivatives of formula (III) include boronic acid esters, such as those described in R. Miyaura *et al*, J. Org. Chem., 1995, 60, 7508-7510. Conveniently, the reaction is carried out in a solvent, such as an ether (e.g. 1,2 dimethoxyethane); in the presence of a base, such as an inorganic base (e.g. sodium carbonate); and employing a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0).

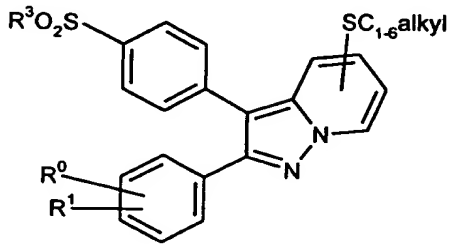
According to a another process (B), compounds of formula (I) wherein R^3 is C_{1-6}alkyl may be prepared by oxidising a compound of formula (IV)



(IV)

or a protected derivative thereof under conventional conditions. Conveniently the oxidation is effected using a monopersulfate compound, such as potassium peroxymonosulfate (known as Oxone™) and the reaction is carried out in a solvent, such as an aqueous alcohol, (e.g. aqueous methanol), and at between -78°C and ambient temperature.

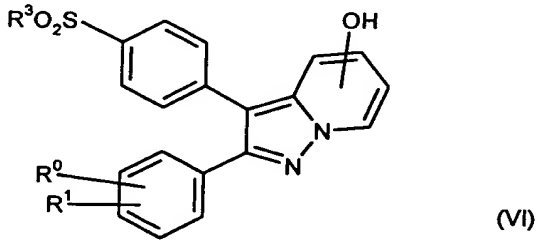
According to a another process (C), compounds of formula (I) wherein R^2 is C_{1-6}alkylsulphonyl may be prepared by oxidising a compound of formula (V)



(V)

or a protected derivative thereof under conventional conditions. Conveniently the oxidation is effected in the manner described just above for process (B).

According to a another process (D), compounds of formula (I) wherein R^2 is C_{1-6}alkoxy substituted by one or more fluorine atoms may be prepared by reacting a phenol of formula (VI)



(VI)

or a protected derivative thereof with a halofluoroalkane under conventional conditions. Conveniently the reaction is effected in a solvent, such as a polar solvent (e.g. **N,N**-dimethylformamide), in the presence of a strong base, such as an inorganic hydride (e.g. sodium hydride), at about ambient temperature and using the appropriate bromofluoroalkane to give the desired compound of formula (I).

According to another process (E) compounds of formula (I) may be prepared by interconversion, utilising other compounds of formula (I) as precursors. The following procedures are illustrative of suitable interconversions.

Compounds of formula (I) wherein R^2 represents C_{1-6}alkyl substituted by one or more fluorine atoms may be prepared from the appropriate compound of formula (I) wherein R^2 is C_{1-6}hydroxyalkyl, C(O)H or $C(O)C_{1-6}$alkyl, by treatment with a suitable source of fluorine. Suitable sources of fluorine include, for example,

diethylaminosulphur trifluoride. Conveniently the reaction is effected in the presence of a solvent, such as a halogenated hydrocarbon (e.g. dichloromethane), and at reduced temperature, such as -78°C.

Compounds of formula (I) wherein R^2 represents C(O)H may be prepared from the corresponding compound of formula (I) wherein R^2 represents CH_2OH by oxidation. Suitable oxidising agents include, for example, manganese (IV) oxide. Conveniently the oxidation is effected in the presence of a solvent, such as a halogenated hydrocarbon (e.g. chloroform), and at elevated temperature (e.g. reflux).

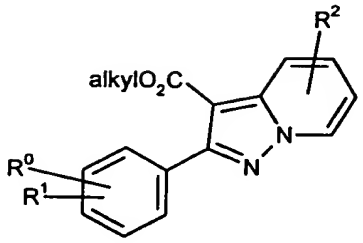
Compounds of formula (I) wherein R^2 represents C_{1-6}hydroxyalkyl, and wherein the hydroxy group is attached to the carbon linked to the pyridine ring, may be prepared by reduction of the compound of formula (I) wherein R^2 represents the corresponding aldehyde or ketone. Suitable reducing agents include hydride reducing agents, such as diisobutylaluminium hydride. Conveniently the reduction is effected in the presence of a solvent, such as a halogenated hydrocarbon (e.g. dichloromethane), and at reduced temperature, such as -78°C.

As will be appreciated by those skilled in the art it may be necessary or desirable at any stage in the synthesis of compounds of formula (I) to protect one or more sensitive groups in the molecule so as to prevent undesirable side reactions.

Another process (F) for preparing compounds of formula (I) thus comprises deprotecting protected derivatives of compounds of formula (I).

The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See, for example, those described in 'Protective Groups in Organic Synthesis' by Theodora W. Green and Peter G M Wuts, second edition, (John Wiley and Sons, 1991), incorporated herein by reference, which also describes methods for the removal of such groups.

Compounds of formula (II) may be prepared by halogenating compounds of formula (VII)

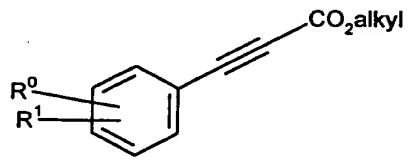


(VII)

by conventional means.

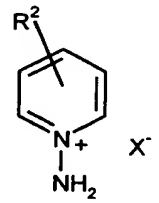
Thus esters of formula (VII) are first hydrolysed to their corresponding acids, for example by treatment with a strong base (e.g. sodium hydroxide), in the present of a solvent (e.g. ethanol) and at elevated temperature. The corresponding acid is then treated with a halogenating agent, conveniently at ambient temperature and in a solvent (e.g. chlorinated hydrocarbon), under which conditions the acid undergoes both halogenation and decarboxylation. Conveniently, the halogenating agent is a brominating agent, such as bromine in the presence of a strong acid (e.g. hydrobromic acid in acetic acid) or N-bromosuccinimide, to yield the corresponding compound of formula (II) wherein Hal is bromine.

Esters of formula (VII) may be prepared by reacting a compound of formula (VIII)



(VIII)

with an aminopyridinium complex of formula (IX)



(IX)

under conventional conditions. Conveniently the reaction is effected in the presence of a base, such as potassium carbonate, a solvent, such as **N,N**-dimethylformamide and at ambient temperature.

Boronic acids of formula (III) are either known compounds or may be prepared by literature methods such as those described in, for example, EPA publication No. 533268.

Compounds of formulae (IV), (V) and (VI) may be prepared by methods analogous to those described for the preparation of the compound of formula (I) from compounds of formula (II).

Compounds of formula (VIII) are either known compounds or may be prepared by literature methods such as those described in, for example, D H Wadsworth *et al*, J Org Chem, (1987), 52(16), 3662-8 and J.Morris and D.G.Wishka, Synthesis (1994), (1), 43-6.

Compounds of formula (IX) are either known compounds or may be prepared by literature methods such as those described in, for example, Y Kobayashi *et al*, Chem Pharm Bull, (1971), 19(10), 2106-15; T. Tsuchiya, J. Kurita and K. Takayama, Chem. Pharm. Bull. 28(9) 2676-2681 (1980) and K Novitskii *et al*, Khim Geterotskil Soedin, 1970 2, 57-62.

Certain intermediates described above are novel compounds, and it is to be understood that all novel intermediates herein form further aspects of the present invention. Compounds of formula (II) are key intermediates and represent a particular aspect of the present invention.

Conveniently, compounds of the invention are isolated following work-up in the form of the free base. Pharmaceutically acceptable acid addition salts of the compounds of the invention may be prepared using conventional means.

Solvates (e.g. hydrates) of a compound of the invention may be formed during the work-up procedure of one of the aforementioned process steps.

The following Examples illustrate the invention but do not limit the invention in any way. All temperatures are in ^{0}C. Flash column chromatography was carried out using Merck 9385 silica. Solid Phase Extraction (SPE) chromatography was carried out using Varian Mega Bond Elut (Si) cartridges (Anachem) under 15mmHg vacuum with stepped gradient elution. Thin layer chromatography (Tlc) was carried out on silica plates. NMR was carried out on a Brucker 400MHz spectrometer. Chemical shifts are given, with respect to tetramethylsilane as internal chemical shift reference, in δ ppm. The following abbreviations are used: Me = methyl, s = singlet, d = doublet, t = triplet and m = multiplet.

Example 1

4-[2-(3-Fluoro-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl]-benzenesulfonamide

i) 3-Trifluoromethyl-pyridin-1-ylideneamine 2,4,6-trimethylphenylsulphonate

Solid t-butoxycarbonyl-O-mesitylenesulfonylhydroxylamine (13.44g 42.5mmol) was added portionwise with stirring to trifluoroacetic acid (TFA) (40ml) over 10min then stirred for a further 30 minutes. The solution was poured onto ice (~250ml) and left until the ice melted. The resulting white solid was filtered off, washed with water, and dissolved in dimethoxyethane (DME) (200ml). The solution was dried over 4 Å mol. sieves for 1.5 hours, filtered, then 3-trifluoromethylpyridine (5g 34mmol) added and the reaction stirred at ambient temperature for 20h. The intermediate salt was isolated by filtration, washed with DME to give the title compound as a white solid (6.63g, 54%).

1H NMR δ (DMSO) 9.34 (1H, s); 9.0 (1H, d, J 6Hz); 8.8(2H, br s); 8.68 (1H, d, J 8Hz); 8.22 (1H, t, J 7Hz); 6.75 (2H, s); 2.17 (3H, s)

ii) 1-(2,2-Dibromo-vinyl)-3-fluoro-benzene

To a stirred, cooled (ice/salt, 0°) solution of carbon tetrabromide (48.82g) in anhydrous CH_2Cl_2 (200ml) was added, portionwise over 3 minutes, triphenylphosphine (77.1g), maintaining the temperature below 10°. The resulting orange suspension was stirred at 0° for 1 hour before adding to it 3-fluorobenzaldehyde (7.8ml). After the addition was complete, the suspension was stirred at 0° for 1 hour then quenched by the addition of water (75ml). The organic phase was separated and washed with brine (75ml), dried (Na_2SO_4) and evaporated to dryness. The residual gum was poured into cyclohexane (1L)

and stirred for 30 minutes. The organic phase was decanted and the residue taken up into CH_2Cl_2 and poured into cyclohexane (1L). This procedure was repeated twice more and the combined organic phases concentrated to ~100ml and passed through silica gel. The filtrate was concentrated to give the title compound as a mobile yellow oil (24g, 100%).
MH+ 280, MH- 279
NMR ($CDCl_3$) δ 7.05 (1H, tm, J= 9Hz) 7.3 (3H, m) 7.45 (1H, s)

iii) (3-Fluoro-phenyl)-propynoic acid methyl ester

To a stirred solution of 1-(2,2-dibromo-vinyl)-3-fluoro-benzene (23.8g) in anhydrous terahydrofuran (THF) (350ml) cooled to -78° was added dropwise over 30 minutes, n-butyllithium (2.2eq, 1.6M in hexanes). The mixture was stirred for a further 30 minutes at -78° before methyl chloroformate (11.6g, 9.5ml) was added and the resultant mixture allowed to warm to 0° for 1hour before being diluted with 1:1 saturated aqueous sodium bicarbonate : ammonium chloride (100ml) and extracted into ether (2x 100ml). The combined organic extract was washed with brine (25ml), dried (Na_2SO_4) and evaporated to dryness to give the title compound as a brown oil (16.7g, 100%).
MH- 173
NMR (CDCl3) δ 7.4-7.1 (4H, m) 3.85 (3H, s, CO_2Me)

iv) 2-(3-Fluoro-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridine-3-carboxylic acid methyl ester

To a solution of (3-fluoro-phenyl)-propynoic acid methyl ester (1.75g, 9.83mmol) and 3-trifluoromethyl-pyridin-1-ylideneamine 2,4,6-trimethylphenylsulphonate (1.87g, 5.17mmol) in CH_3CN (15ml) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (1.47ml) and the mixture heated to reflux for 30 minutes. The reaction was concentrated *in vacuo*, poured into water and extracted into ethyl acetate (2x50ml). The combined organic phases were washed with water (20ml), dried and purified by column chromatography with cyclohexane/ethyl acetate (EtOAc) (20:1) as eluant. This gave the title compound as a white solid (448mg, 26%).
1H NMR ($CDCl_3$) δ 8.9 (1H, s); 8.35 (1H, d, J 9Hz); 7.60 (2H, 2x d, J 8Hz); 7.55 (1H, d, J 10Hz); 7.45 (1H, dt, J 8 & 6Hz); 7.20(1H, dt, J 8&2Hz); 3.89 (3H, s)

v) 2-(3-Fluoro-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridine-3-carboxylic acid

To a suspension of 2-(3-fluoro-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridine-3-carboxylic acid methyl ester (448mg) in ethanol (10ml) was added 2N NaOH and heated at reflux for 3h. The cooled reaction mixture was acidified with 2N HCl and the resulting solid isolated by filtration and dried *in vacuo* at 60° to give the title compound as an off-white solid (403mg, 93%).

MH+ = 323

1H NMR (DMSO) δ 9.55 (1H, s); 8.3 (1H, d); 7.8 (1H, d); 7.65 (2H, 2x d); 7.55 (1H, m); 7.35 (1H, t)

vi) 3-Bromo-2-(3-fluoro-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridine

To a solution of 2-(3-fluoro-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridine-3-carboxylic acid (403mg, 1.24mmol) and $NaHCO_3$ (355mg, 3.4eq) in dimethyl formamide (DMF) (10ml) was added N-bromosuccinimide (1.1eq, 244mg) and the resulting solution stirred at rt for 1.5h. The mixture was diluted with water and extracted with EtOAc (3x10ml). The combined organic phases were washed with water (3x10ml), dried and concentrated *in vacuo* to give the title compound as a brown solid (390mg, 85%).

MH+ 358/359

1H NMR (CDCl3) 8.8 (1H, s); 7.9 (1H, d); 7.8 (1H, d); 7.65 (1H, d); 7.50 (1H, m); 7.35 (1H, d); 7.15 (1H, t)

vii) 4-[2-(3-Fluoro-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl]-benzenesulfonamide

A mixture of 4-iodobenzenesulphonamide (651mg); dipinacoldiborane[1] (495mg); potassium acetate (860mg); and [1,1'-bis(diphenylphosphino)-ferrocene]palladium(II) chloride complex : dichloromethane (1:1) (50mg); in dimethylformamide (5ml) was heated under nitrogen at 80° for 1.5 h. To the cooled reaction mixture was added 3-bromo-2-(3-fluoro-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridine (330mg, 0.919mmol), 2N Na_2CO_3 (4ml) and tetrakis(triphenylphosphine)palladium (0) (40mg) and the mixture heated at reflux under nitrogen for 18 hours. The cooled reaction mixture was poured into water (30ml) and the suspension extracted with ethyl acetate (3x20ml). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by SPE chromatography eluting with a gradient of cyclohexane:EtOAc (100: 0 to 0:100, 10% step). Trituration of the concentrated

fractions containing product with diethyl ether gave the title compound as a white solid (139mg, 35%).

MH+ 436

1H ($CDCl_3$) 8.87 (1H, s); 8.0 (2H, d, J 8Hz); 7.65 (1H, d, J 9Hz); 7.50 (2H, d, J 8Hz); 7.35 (4H, m); 7.10 (1H, t, J 8Hz); 4.88 (2H, br s)

Ref: [1] R. Miyaura et al J.Org.Chem.,1995,60,7508-7510

Example 2

2-(3-Fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridine

To a solution of the 3-bromo-2-(3-fluoro-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridine (50mg, 0.139mmol) in DMF (5ml) was added 4-methanesulfonyl-phenylboronic acid (37mg, 1.3eq), ground potassium phosphate (83mg) and tetrakis(triphenylphosphine)palladium (0) (10mg) and the mixture heated to 90° for 18h under N_2. The cooled mixture was poured into water (10ml) and extracted into EtOAc (4x 10ml). The combined organic phases were washed sequentially with water, brine, 2N NaOH and brine, dried and concentrated *in vacuo* to give the title compound as an off-white solid (27mg, 45%).

MH+ 435

$_1$H NMR ($CDCl_3$) δ 8.9 (1H, s); 8.0 (2H, d, J 8Hz); 7.65 (1H, d, J 9Hz); 7.55 (2H, d, J 8Hz); 7.25-7.4 (3H, m); 7.1(1H, m); 3.15 (3H, s)

Example 3

4-[2-(4-Ethoxy-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl]-benzenesulfonamide

By using 4-ethoxybenzaldehyde the title compound was obtained as white solid (127mg, 44%) in the manner described for Example 1.

MH+ 462

1H NMR ($CDCl_3$) δ 8.85 (1H, s); 7.95 (2H, d, J 8Hz); 7.60 (1H, d, J 9Hz); 7.52 (2H, d, 8Hz); 7.47 (2H, d, J 8Hz); 7.3 (1H, dd, J (&2Hz); 6.9 (2H, d, J 9Hz); 4.86 (2H, br s); 4.07 (2H, q, J 7Hz); 1.45 (3H, t, J 7Hz)

Example 4

4-[2-(4-Fluoro-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl]-benzenesulfonamide

By using 4-fluorobenzaldehyde the title compound was obtained as a brown solid (240mg, 70%) in the manner described for Example 1.

MH+ 436

1H NMR (CDCl3) δ 8.85 (1H, s); 8.0 (2H, d, J 8Hz); 7.65 (1H, d, J 9Hz); 7.5 (4H, m), 7.33 (1H, dd, J 9&1Hz); 7.1 (2H, t, 8Hz); 5.0 (2H, br s)

Example 5

2-(4-Fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridine

By using 3-bromo-2-(4-fluoro-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridine the title compound was obtained as a white solid (95mg, 48%) in the manner described in Example 2.

MH+ =435

1H NMR ($CDCl_3$) δ 8.87 (1H, s); 8.0 (2H, d, J 8Hz); 7.67 (1H, d, J 9Hz); 7.55 (4H, m); 7.35 (1H, dd, J 9&1Hz); 7.1 (2H, t, J 9Hz); 3.15 (3H, s)

Example 6

4-(2-Phenyl-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl)-benzenesulfonamide

By using phenyl propynoic acid methyl ester (LANCASTER) the title compound was obtained as a white solid (140mg, 43%) in the manner described in Example 1.

MH+ 418

1H NMR (CDCl3) δ 8.85 (1H, s); 7.95 (2H, d, J 8Hz); 7.65 (1H, d, J 9Hz) 7.53 (3H, m); 7.4 (4H, m) 4.86 (2H, br s)

Example 7

3-(4-Methanesulfonyl-phenyl)-2-phenyl-6-trifluoromethyl-pyrazolo[1,5-a]pyridine

By using 3-bromo-2-phenyl-6-trifluoromethyl-pyrazolo[1,5-a]pyridine the title compound was obtained as an off-white solid (21mg, 34%) in the manner described in Example 2.

MH+ 417

1H NMR (CDCl3) δ 8.87 (1H, s); 7.97 (2H, d, 8Hz); 7.67 (1H, d, J 9Hz); 7.55 (4H, m); 7.4 (4H, m); 3.15 (3H, s)

Example 8

4-[2-(4-methyl-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl]-benzenesulfonamide

By using 4-methylbenzaldehyde the title compound is prepared in the manner described above for Example 1.

Biological Data

Inhibitory activity against human COX-1 and COX-2 was assessed in COS cells which had been stably transfected with cDNA for human COX-1 and human COX-2. 24 Hours prior to experiment, COS cells were transferred from the 175cm^2 flasks in which they were grown, onto 24-well cell culture plates using the following procedure. The incubation medium (Dulbecco's modified eagles medium (DMEM) supplemented with heat-inactivated foetal calf serum (10%v/v), penicillin (100 IU/ml), streptomycin (100μg/ml) and geneticin (600μg/ml)) was removed from a flask of confluent cells (1 flask at confluency contains approximately 1x10^7 cells). 10ml of phosphate buffered saline (PBS) was added to the flask to wash the cells. Having discarded the PBS, cells were then rinsed in 10ml trypsin for 20 seconds, after which the trypsin was removed and the flask placed in an incubator (37°) for 1-2 minutes until cells became detached from the flask. The flask was then removed from the incubator and cells resuspended in 10ml of fresh incubation medium. The contents of the flask was transferred to a 250ml sterile container and the volume of incubation medium subsequently made up to 100ml. 1ml cell suspension was pipetted into each well of 4x24-well cell culture plates. The plates were then placed in an incubator (37°C, 95% air/5% CO_2) overnight. If more than 1 flask of cells were required, the cells from the individual flasks were combined before being dispensed into the 24-well plates.

Following the overnight incubation, the incubation medium was completely removed from the 24-well cell culture plates and replaced with 250μl fresh DMEM (37°C). The test compounds were made up to 250x the required test concentration in DMSO and were added to the wells in a volume of 1μl. Plates were then mixed gently by swirling and then placed in an incubator for 1 hour (37°C, 95% air/5% CO_2). Following the incubation period, 10μl of arachidonic acid (750μM) was added to each well to give a final arachidonic acid concentration of 30μM. Plates were then incubated for a further 15 minutes,

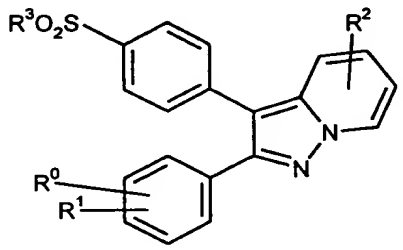
after which the incubation medium was removed from each well of the plates and stored at -20°C, prior to determination of prostaglandin E_2 (PGE2) levels using enzyme immunoassay. The inhibitory potency of the test compound was expressed as an IC_{50} value, which is defined as the concentration of the compound required to inhibit the PGE2 release from the cells by 50%. The selectivity ratio of inhibition of COX-1 versus COX-2 was calculated by comparing respective IC_{50} values.The following IC_{50} values for inhibition of COX-2 and COX-1 were obtained for compounds of the invention:

Example No.	COX-2: IC_{50}(nM)	COX-1: IC_{50}(nM)
1(v)	34	>100,000
2	548	>100,000
3	34	32,200
4	34	>100,000
5	26	>100,000
6	31	26350
7	30	>100,000

The application of which this specification forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any novel feature or combination of features relating to the invention described herein. They may take the form of product, process or use claims and may include, by way of example and without limitation, the following claims:

Claims

1. Compounds of formula (I)



(I)

and pharmaceutically acceptable derivatives thereof in which:

R^0 and R^1 are independently selected from H, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{1-6}alkoxy substituted by one or more fluorine atoms;
R^2 is H, C_{1-6}alkyl, C_{1-6}alkyl substituted by one or more fluorine atoms, C_{1-6}alkoxy, C_{1-6}hydroxyalkyl, SC_{1-6}alkyl, C(O)H, $C(O)C_{1-6}$alkyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxy substituted by one or more fluorine atoms; and
R^3 is C_{1-6}alkyl or NH_2.

2. Compounds as claimed in claim 1 wherein R^0 and R^1 are independently H, halogen, C_{1-6}alkyl, or C_{1-6}alkoxy; R^2 is C_{1-3}alkyl substituted by one or more fluorine atoms; and R^3 is C_{1-3}alkyl or NH_2..

3. Compounds as claimed in claim 1 or 2 wherein R^0 and R^1 are independently H, F, Cl, C_{1-3}alkyl (e.g. methyl), or C_{1-3}alkoxy (e.g. ethoxy); R^2 is C_{1-3}alkyl substituted by one or more fluorine atoms (e.g. trifluoromethyl); and R^3 is methyl or NH_2.

4. Compounds as claimed in any one of claims 1 to 3 wherein R^0 is F, Cl, or C_{1-3}alkyl (e.g. methyl) or C_{1-3}alkoxy (e.g. ethoxy); R^1 is H; R^2 is C_{1-3}alkyl

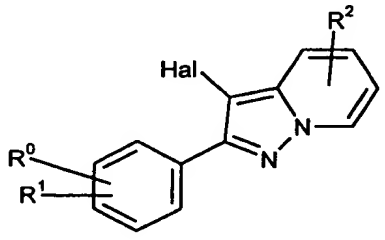
substituted by one or more fluorine atoms (e.g. trifluoromethyl); and R^3 is methyl or NH_2.

5. Compounds as claimed in any one of claims 1 to 4 wherein R^0 is at the 3- or 4- position of the phenyl ring; and R^2 is at the 6- position of the pyridine ring.

6. 4-[2-(3-fluoro-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl]-benzenesulfonamide;
2-(3-fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridine;
4-[2-(4-ethoxy-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl]-benzenesulfonamide;
4-[2-(4-fluoro-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl]-benzenesulfonamide;
2-(4-fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridine;
4-(2-phenyl-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl)-benzenesulfonamide;
3-(4-methanesulfonyl-phenyl)-2-phenyl-6-trifluoromethyl-pyrazolo[1,5-a]pyridine;
4-[2-(4-methyl-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl]-benzenesulfonamide;
and pharmaceutically acceptable derivatives thereof.

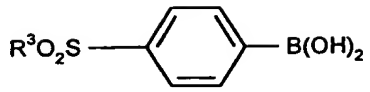
7. A process for the preparation of compound of formula (I) and pharmaceutically acceptable derivatives thereof as defined in any one of claims 1 to 6, which comprises:

(A) reacting a compound of formula (II)



(II)

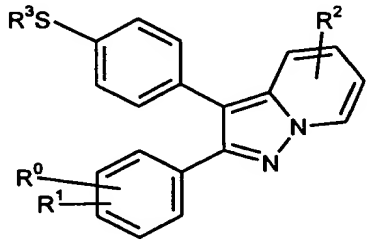
or a protected derivative thereof, with a compound of formula (III)



(III)

or a protected derivative thereof; or

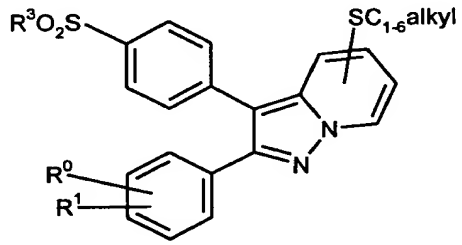
(B) where R^3 represents C_{1-4}alkyl, reacting a compound of formula (IV)



(IV)

or a protected derivative thereof with an oxidising agent; or

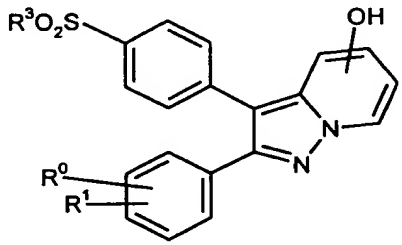
(C) where R^2 is C_{1-6}alkylsulphonyl, oxidising a compound of formula (V)



(V)

or a protected derivative; or

(D) where R^2 is C_{1-6}alkoxy substituted by one or more fluorine atoms, reacting a alcohol of formula (VI)



(VI)

or a protected derivative thereof with a halofluoroalkane; or

(E) interconversion of a compound of formula (I) into another compound of formula (I); or

(F) deprotecting a protected derivative of compound of formula (I);

and optionally converting compounds of formula (I) prepared by any one of processes (A) to (F) into pharmaceutically acceptable derivatives thereof.

8. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof as defined in any one of Claims 1 to 6 in admixture with one or more physiologically acceptable carriers or excipients.

9. A compound of formula (I) or a pharmaceutically acceptable derivative thereof as defined in any one of Claims 1 to 6 for use in human or veterinary medicine.

10. A compound of formula (I) or a pharmaceutically acceptable derivative thereof as defined in any one of Claims 1 to 6 for use in the treatment of a condition which is mediated by selective inhibition of COX-2.

11. A method of treating a human or animal subject suffering from a condition which is mediated by selective inhibition of COX-2 which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative as defined in any one of Claims 1 to 6.

14. The use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof as defined in any one of Claims 1 to 6 for the manufacture of a therapeutic agent for the treatment of a condition which is mediated by selective inhibition of COX-2.